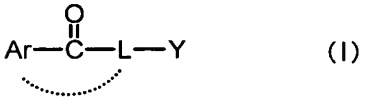
CLAIMS

1. A preventive or therapeutic agent for voiding disturbance, which comprises a compound having both of an acetylcholinesterase inhibitory action and an α1 antagonistic action.

2. The agent according to claim 1, which comprises a compound having both of an acetylcholinesterase inhibitory action and an α1 antagonistic action represented by the formula:



(I)

wherein Ar represents an optionally condensed 5- or 6-membered aromatic ring group and said aromatic ring group may have a substituent, L represents a spacer having a main chain of 1 to 10 of atoms which may have a substituent, or may form a ring with Ar, and Y represents an amino group which may have a substituent or a nitrogen-containing heterocyclic group which may have a substituent, or a salt thereof or a prodrug thereof.

3. The agent according to claim 2, wherein L is a C_{1-10} alkylene group which may have a substituent.

4. The agent according to claim 1, which is a preventive or therapeutic agent for voiding disturbance accompanied with benign prostatic hyperplasia.

5. The agent according to claim 1, wherein an IC_{50} value

of each of an acetylcholinesterase inhibitory action and an α1 antagonistic action of the compound is a ratio of about 1:100 to about 100:1.

6. The agent according to claim 1, wherein an IC_{50} value of each of an acetylcholinesterase inhibitory action and an α1 antagonistic action of the compound is a ratio of about 1:1 to about 30:1.

7. The agent according to claim 1, which does not exhibit reduction of blood pressure at a dose exhibiting an effect of improving urine flow rate.

8. The agent according to claim 7, wherein a reduction of blood pressure after administration is within about 10% relative to that before administration at a dose in which a urine flow rate after administration is improved by about 20% or more relative to that before administration.

9. The agent according to claim 1, which does not exhibit reduction of blood pressure at a dose exhibiting an effect of improving voiding efficiency.

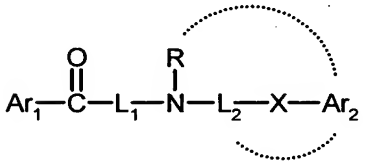
10. The agent according to claim 9, wherein reduction of blood pressure after administration is within about 10% relative to that before administration at a dose that a voiding efficiency after administration is improved by about 10% or more relative to that before administration.

11. The agent according to claim 1, wherein orthostatic hypotension is not accompanied.

12. A method for preventing or treating voiding disturbance, which comprises administering an effective amount of a compound having both of an acetylcholinesterase inhibitory action and an α1 antagonistic action to a mammal.

13. Use of a compound having both of an acetylcholinesterase inhibitory action and an α1 antagonistic action for preparing a preventive or therapeutic agent for voiding disturbance.

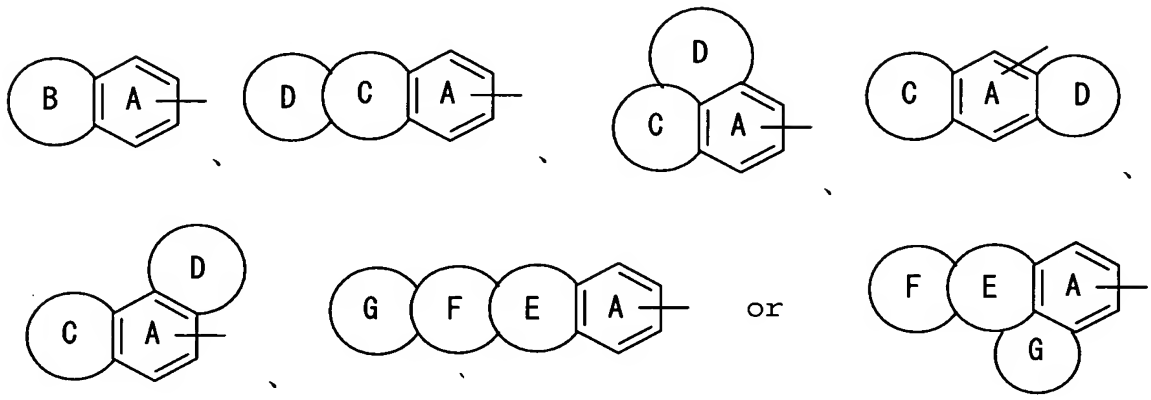
14. A compound represented by the formula:



(Ia)

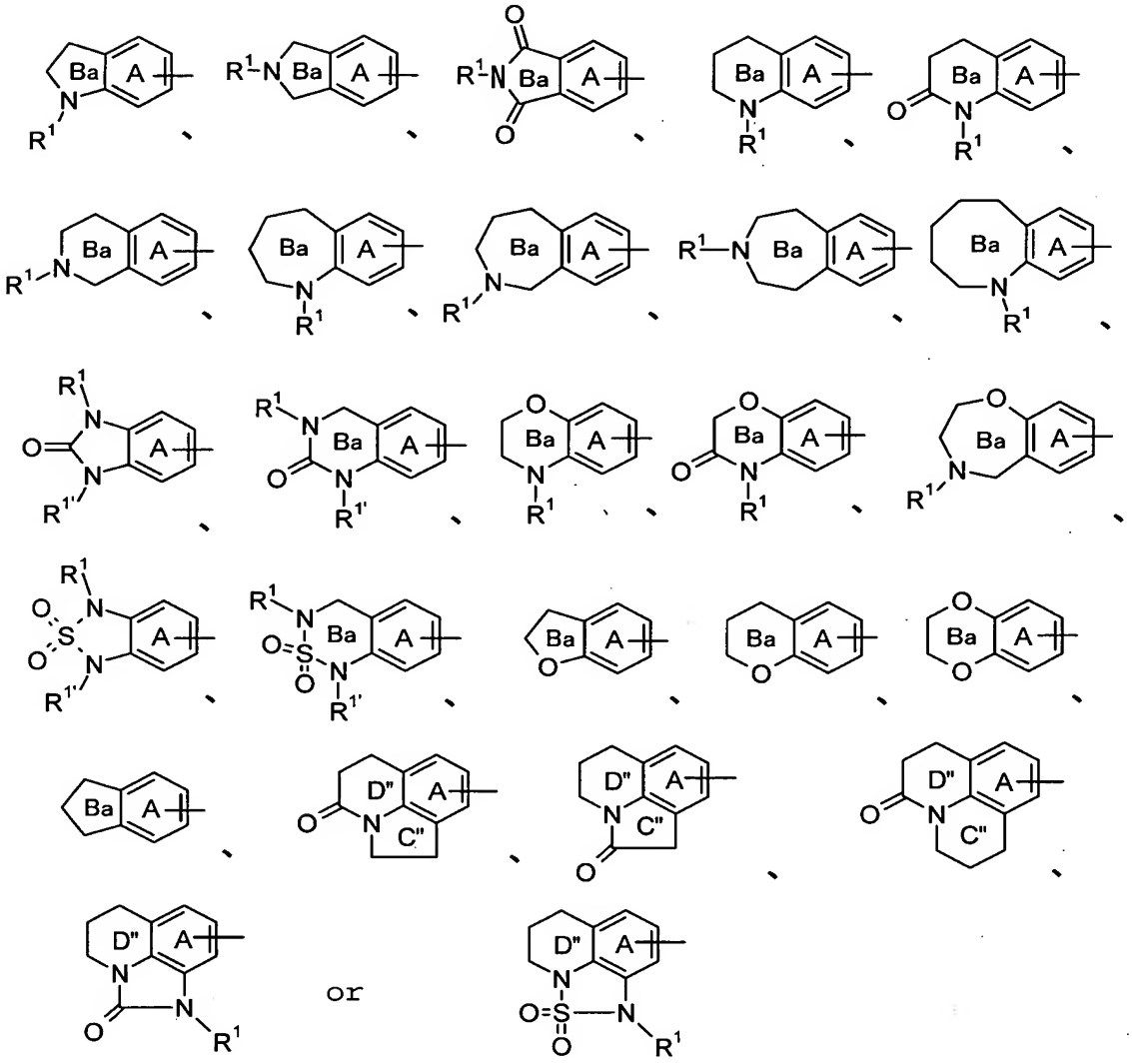
wherein Ar_1 represents a di- to tetra-cyclic condensed benzene ring group which may have a substituent, L_1 represents a C_{4-6} alkylene group which may have a substituent, L_2 represents a C_{2-4} alkylene group which may have a substituent, R represents a hydrogen atom or a hydrocarbon group which may have a substituent, X represents a bond, an oxygen atom or NR^{1a} (wherein R^{1a} represents a hydrogen atom, a hydrocarbon group which may have a substituent, an acyl group or a heterocyclic group which may have a substituent), and Ar_2 represents an aromatic ring group which may have a substituent, or Ar_2 and R, or Ar_2 and L_2 may link together to form a ring, or a salt thereof.

15. The compound according to claim 14, wherein Ar_1 is a group represented by the formula:



wherein A ring represents a benzene ring which may have a substituent, B ring represents a homocyclic ring or a heterocyclic ring which may have a substituent, one of C ring and D ring represents a heterocyclic ring which may have a subtituent, the other represents a 5- to 9-membered ring which may have a substituent, and at least one ring of E ring, F ring and G ring represents a heterocyclic ring which may have a substituent and the other rings represent a 5- to 9- membered ring which may have a substituent.

16. The compound according to claim 14, wherein Ar_1 is a group represented by the formula:



wherein A ring represents a benzene ring which may have a substituent, Ba ring represents a homocyclic ring or a heterocyclic ring which may have a substituent, C″ ring and D″ ring represent a nitrogen-containing heterocyclic ring which may have a substituent respectively, $R^1$and $R^{1'}$ represent a hydrogen atom, a hydrocarbon group which may have a substituent, an acyl group or a heterocyclic group which may have a substituent respectively.

17. The compound according to claim 16, wherein A ring represents a benzene ring which may have 1 or 2 substituent(s) selected from aminosulfonyl, mono- or di-C_{1-6} alkylaminosulfonyl, carbamoyl and mono- or di-C_{1-6} alkylcarbamoyl, Ba ring, C" ring and D" ring may have 1 or 2 substituent(s) selected from C_{1-6} alkyl, C_{1-6} alkylcarbonylamino and C_{1-6} alkylsulfonylamino, respectively, and R^1 and $R^{1'}$ represent (1) a hydrogen atom, (2) a C_{1-6} alkyl group or a C_{7-16} aralkyl group, each of which may have 1 or 2 sustituent(s) selected from hydroxy and C_{1-6} alkoxycarbonyl, or (3) formula $-(C=O)-R^{2'}$, $-(C=O)-NR^{2'}R^{3'}$ or $-SO_2R^{2'}$ [wherein $R^{2'}$ and $R^{3'}$ represent hydrogen atom, optionally halogenated C_{1-6} alkyl or C_{6-10} aryl, respectively].

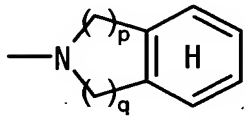
18. The compound according to claim 14, wherein R is a hydrogen atom or a C_{1-4} alkyl group.

19. The compound according to claim 14, wherein L_1 is a C_{4-5} alkylene group, and L_2 is a C_{2-3} alkylene group which may have phenyl, hydroxy or oxo.

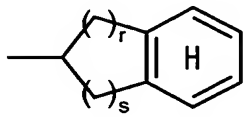
20. The compound according to claim 14, wherein Ar_2 is a C_{6-10} aryl group or a 5- or 6-membered aromatic heterocyclic group (optionally condensed with a benzene ring) containing 1 to 4 hetero atom(s) selected from a nitrogen atom, an oxygen atom and a sulfur atom, each of which may have 1 to 3 substituent(s) selected from halogen, nitro, hydroxy, optionally halogenated C_{1-6} alkyl, optionally halogenated

C_{1-6} alkoxy and aminosulfonyl.

21. The compound according to claim 14, wherein the ring formed by linking Ar_2 and R together is a ring represented by the formula:

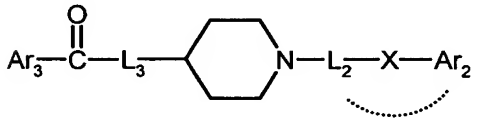


wherein p and q represent an integer of 1 to 3, respectively, and H ring represents a benzene ring which may have 1 to 3 substituent(s) selected from halogen, hydroxy, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy, and the ring formed by linking Ar_2 and L_2 together is a ring represented by the formula:



wherein r represents an integer of 0 to 2, s represents an integer of 1 to 3 and r+s is an integer of 2 to 5, and H ring represents a benzene ring which may have 1 to 3 substituents(s) selected from halogen, hydroxy, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy.

22. A compound represented by the formula:

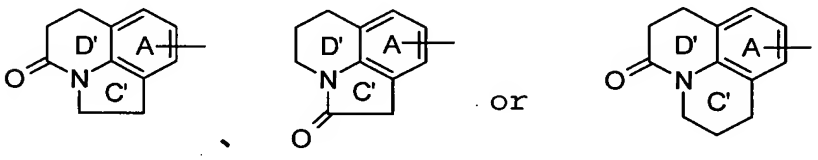


(Ib)

wherein Ar_3 represents a benzimidazole ring group, a

quinazoline ring group, a 1,4-benzoxazine ring group or a tricyclic to tetracyclic condensed benzene ring group, each of which may have a substituent, L_3 represents a C_{2-4} alkylene group which may have a substituent, L_2 represents a C_{2-4} alkylene group which may have a substituent, X represents a bond, an oxygen atom or NR^{1a} (wherein R^{1a} represents a hydrogen atom, a hydrocarbon group which may have a substituent, an acyl group or a heterocyclic group which may have a substituent), and Ar_2 represents an aromatic ring group which may have a substituent, or Ar_2 and L_2 may link together to form a ring, or a salt thereof.

23. The compound according to claim 22, wherein Ar_3 is a group represented by the formula:

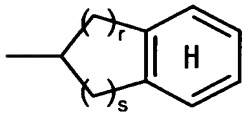


wherein A ring represents a benzene ring which may have a substituent, and C' ring and D' ring represent a nitrogen-containing heterocyclic ring which may have a substituent in addition to an oxo group, respectively.

24. The compound according to claim 22, wherein L_3 is an ethylene group, L_2 is a C_{2-3} alkylene group which may have phenyl, hydroxy or oxo, and X is a bond or an oxygen atom.

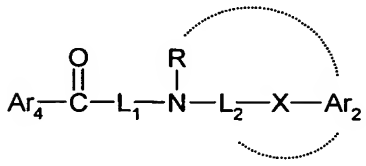
25. The compound according to claim 22, wherein Ar_2 is a C_{6-10} aryl group or a 5- or 6-membered aromatic heterocyclic

group (optionally condensed with a benzene ring) containing 1 to 4 hetero atom(s) selected from a nitrogen atom, an oxygen atom and a sulfur atom, each of which may have 1 to 3 substituent(s) selected from halogen, nitro, hydroxy, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and aminosulfonyl, and the ring formed by linking Ar_2 and L_2 together is a ring represented by the formula:



wherein r represents an integer of 0 to 2, s represents an integer of 1 to 3 and r+s is an integer of 2 to 5, and H ring represents a benzene ring which may have 1 to 3 substituents(s) selected from halogen, hydroxy, optionally halogenated C_{1-6} alkyl and optionally halogenated C_{1-6} alkoxy.

26. A compound represented by the formula:



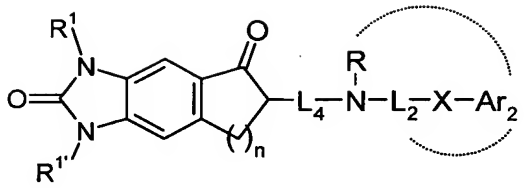
(Ic)

wherein Ar_4 represents a benzene ring group having 1 or 2 substituent(s) selected from aminosulfonyl, mono- or di-C_{1-6} alkylaminosulfonyl, C_{1-6} alkyl-carbonylamino and C_{1-6} alkylsulfonylamino, and optionally further having 1 to 4 substituent(s), L_1 represents a C_{4-6} alkylene group which may have a substituent, L_2 represents a C_{2-4} alkylene group

which may have a substituent, R represents a hydrogen atom or a hydrocarbon group which may have a substituent, X represents a bond, an oxygen atom or NR^{1a} (wherein R^{1a} represents a hydrogen atom, a hydrocarbon group which may have a substituent, an acyl group or a heterocyclic group which may have a substituent), and Ar_2 represents an aromatic ring group which may have a substituent, or Ar_2 and R, or Ar_2 and L_2 may link together to form a ring, or a salt thereof.

27. The compound according to claim 26, wherein Ar_4 is a benzene ring group having 1 or 2 substituent(s) selected from aminosulfonyl, mono- or di-C_{1-6} alkylaminosulfonyl, C_{1-6} alkyl-carbonylamino and C_{1-6} alkylsulfonylamino, and optionally further having 1 or 2 C_{1-4} alkoxy(s), L_1 is a C_{4-5} alkylene group, L_2 is a C_{2-3} alkylene group optionally having hydroxy or oxo, R is a hydrogen atom or a C_{1-4} alkyl group, X is a bond, and Ar_2 is a C_{6-10} aryl group or a 5- or 6-membered aromatic heterocyclic group (optionally condensed with a benzene ring) containing 1 to 4 hetero atom(s) selected from a nitrogen atom, an oxygen atom and a sulfur atom, each of which may have 1 to 3 substituent(s) selected from halogen, nitro, hydroxy, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and aminosulfonyl.

28. A compound represented by the formula:



(Id)

wherein R^1 and $R^{1'}$ represent a hydrogen atom, a hydrocarbon group which may have a substituent, an acyl group or a heterocyclic group which may have a substituent, n represents an integer of 1 or 2, L_4 represents a C_{3-5} alkylene group which may have a substituent, L_2 represents a C_{2-4} alkylene group which may have a substituent, R represents a hydrogen atom or a hydrocarbon group which may have a substituent, X represents a bond, an oxygen atom or NR^{1a} (wherein R^{1a} represents a hydrogen atom, a hydrocarbon group which may have a substituent, an acyl group or a heterocyclic group which may have a substituent), and Ar_2 represents an aromatic ring group which may have a substituent, or Ar_2 and R, or Ar_2 and L_2 may link together to form a ring, or a salt thereof.

29. The compound according to claim 28, wherein R^1 and $R^{1'}$ are a hydrogen atom or an optionally halogenated C_{1-6} alkyl group, respectively, L_4 is a C_{3-4} alkylene group, L_2 is a C_{2-3} alkylene group which may have hydroxy or oxo, R is a hydrogen atom or a C_{1-4} alkyl group, X is a bond, and Ar_2 is a C_{6-10} aryl group or a 5- or 6-membered aromatic heterocyclic ring group (optionally condensed with a benzene ring) containing 1 to 4 hetero atom(s) selected

from a nitrogen atom, an oxygen atom and a sulfur atom, each of which may have 1 to 3 substituent(s) selected from halogen, nitro, hydroxy, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy and aminosulfonyl.

30. 8-(5-[[2-(2-chlorophenyl)ethyl]amino]pentanoyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof,

5-[5-[[2-(2-chlorophenyl)ethyl](methyl)amino]pentanoyl]-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one or a salt thereof,

1,3-dimethyl-5-[5-({2-[2-(trifluoromethoxy)phenyl]ethyl}amino)pentanoyl]-1,3-dihydro-2H-benzimidazol-2-one or a salt thereof,

8-{5-[[2-(2-methoxyphenyl)ethyl](methyl)amino]pentanoyl}-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one or a salt thereof,

8-{5-[[2-(2-methoxyphenyl)ethyl](methyl)amino]pentanoyl}-1-methyl-5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2(1H)-one or a salt thereof,

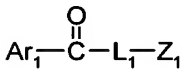
1,3-dimethyl-5-[5-({2-[2-(trifluoromethoxy)phenyl]ethyl}amino)pentanoyl]-1,3-dihydro-2H-benzimidazol-2-one or a salt thereof,

8-(5-{[2-(2-chlorophenyl)ethyl]amino}pentanoyl)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one or a salt thereof, or

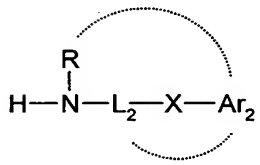
5-(5-{[2-(2-chlorophenyl)ethyl]amino}pentanoyl)-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one or a salt thereof.

31. A prodrug of the compound according to any one of claims 14, 22, 26 and 28 or a salt thereof.

32. A process for preparing the compound according to claim 14, which comprises reacting a compound represented by the formula:

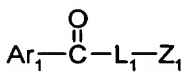


wherein Z_1 represents a leaving group, and the other respective symbols are as defined in claim 14, or a salt thereof with a compound represented by the formula:



wherein respective symbols are as defined in claim 14, or a salt thereof.

33. A process for preparing the compound represented by the formula:

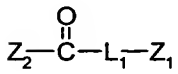


wherein Z_1 represents a leaving group, and the other respective symbols are as defined in claim 14, or a salt thereof, which comprises reacting a compound represented by

the formula:

Ar_1-H

wherein Ar_1 is as defined in claim 14, or a salt thereof with a compound represented by the formula:



wherein Z_2 represents a leaving group, Z_1 is as defined above, and L_1 is as defined in claim 14, or a salt thereof.

34. The process according to claim 33, wherein zinc chloride is used as a catalyst and nitroalkane is used as a solvent.

35. A medicine comprising the compound according to any one of claims 14, 22, 26 and 28 or a salt thereof or a prodrug thereof.

36. The medicine according to claim 35, which is a preventive or therapeutic agent for voiding disturbance.

37. The medicine according to claim 35, which is a preventive or therapeutic agent for voiding disturbance accompanied with benign prostatic hyperplasia.

38. The medicine according to claim 37, which is a preventive or therapeutic agent for voiding disturbance due to detrusor underactivity.

39. A method for preventing or treating voiding disturbance, which comprises administering an effective amount of the compound according to any one of claims 14,

22, 26 and 28 or a salt thereof or a prodrug thereof to a mammal.

40. Use of the compound according to any one of claims 14, 22, 26 and 28 or a salt thereof or a prodrug thereof for preparing a preventive or therapeutic agent for voiding disturbance.

41. A method for screening a compound having a voiding disturbance preventing or treating effect by Pressure Flow Study, which comprises using an animal model loaded with an α agonist.

42. The screening method according to claim 41, wherein the α agonist is phenylephrine.

43. A compound having a voiding disturbance preventing or treating effect obtained by the screening method according to claim 41, or a salt thereof.